Author's response to reviews

Title: Syndymics of syphilis, HCV infection, and methamphetamine use along the east coast of China.

Authors:

meizhen liao (liaomz161@126.com)
dianmin kang (hivjiance@126.com)
xiaorun tao (hivjiance@126.com)
yuesheng qian (hivjiance@126.com)
guoyong wang (hivjiance@126.com)
cui yang (cyang@jhsp.edu)
xiaoyan zhu (hivjiance@126.com)
na zhang (hivjiance@126.com)
zhenqiang bi (bzq63@163.com)
yujiang jia (jiayj@aol.com)

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Author's response to reviews: see over
Dear Editor,

We are grateful to you offering us the revision opportunity. Thanks so much for the reviewers for their insightful comments. Following your guidance, we have revised the manuscript in light of the reviewer’s suggestions. We provided a point-by-point responses to the issues raised by the reviewers.

REVIEWER #1:

Point 1.1 Prior to publication the entire manuscript needs to be copy-edited in detail to improve clarity, and quality of writing. English grammar. The text needs to be more carefully edited.

Thanks for reviewer’s suggestion. The style and format were revised following the journal requirement. We have also improved the writing and check the grammar errors.

Point 1.2 Recruitment details. The recruitment procedure is not very clear. The author mentioned ‘socio-demographic mapping strategy’, ‘community outreach’, ‘venue-based recruitment’, and ‘peer referrals’, but we do need some detail information on how the sample was recruited.

We apologize for the oversight of initial submission. Prior to the recruitment of the participants of the survey, we conducted in-depth interviews using key informants to gather the background information about drug users, which helped the sampling frame development. After these initial study participants were approached and interviewed after eligibility assessment, we asked the participants to refer their peers to attend this study. All potential participants were invited for eligibility assessment. A part of participants didn’t want to visit the fixed interview site due to illegal practice of drug abuse in China, so the trained health professional conducted the interview in community or venues such as, hotel, bar, etc. Hence, mixed methods of community outreach and venue-based recruitment were also applied in the study. Interviews were conducted by trained health professionals. Revisions were made in lines 2-5 for the recruitment details in the Method section, Recruitment and Participants on page 5.

Point 1.3 Testing results informed. Whether the participants were informed about the testing results? There is no information in this manuscript. If informed, how? After informed, how about the referrals and treatment?

All the participants were informed their testing results of HIV, syphilis and HCV by trained health professionals. All of the notification of infection testing results and
referrals for positive individuals to health care services were also provided with a confidential way using prior signed unique code. We didn’t collect the treatment result in this surveillance program and will collect the information in our next survey. The revisions were made in the last 5 lines in the session of “measures” on page 7.

**Point 1.4 Regular partner. How to define the regular sex partners?**

The regular sex partners refer to their wife/husband or the sex partners not get married but live together.

**Point 1.5 Typo. There are many typos in this paper, please check it carefully. For example, the study cities were Jinan and Qingdao in the methods/recruitment and participants part, but the study cities were Jining and Qingdao in the results/correlates for syphilis and HCV infection part and the Tables 1/2;**

Many thanks for the reviewer’s suggestions. The study cities were Jining and Qindao. The revision was made in line 1 of Method section on page 5.

**Point 1.6 Data. Please check your data again, some data are not clear. For example, in the results/Characteristics of participants part, it mentioned “28% single, 70.2% currently married or cohabiting and 1.9% divorced or widowed”. If we add these three percentages, it will be 100.1%. The same problems existed in the tables as well. In the table 1, for the variables “Types of drugs” and “injected drug use”, I think the third column is the col%, but these the sum of the percent is not 100%.**

Many thanks for the reviewer’s comments. Because the variables “types of drugs” and “injected drug use” were multi-choice variables, the percentages will not be added to 100%. The revision was made in the Table 1.

**REVIEWER #2:**

**Compulsory revisions:**

**Point 2.1 Manuscript needs revision by an English editor. The manuscript would benefit from overall strengthening of the introduction, Clarification on methods, more concise presentation of results.**

Many thanks for the reviewer’s comments. We have native English speaker checked and edited the entire manuscript. We made the further revision to strengthen the introduction and clarify the methods according to reviewer’s suggestion, and we also made additional analyses to describe the factor of unprotected sex with commercial sex partners in last year in Table 1 and its correlates in Table 2, the most important results from the tables was described in the Result section.

**Point 2.2 Additional analyses of drug use and risky sexual behavior are necessary for the conclusion drawn by the authors.**
We followed the reviewer’s suggestion and added a column in the Tables 1/2 to describe the factor of unprotected sex with commercial sex partners in last year.

**Point 2.3 This discussion/conclusion was not always based on the results of this study.**

We made revisions on the second paragraph in the Discussion section based on the results and deleted some unrelated content in lines 9 and 11 on page 9, and lines 3 on page 10.

**Background. Minor essential revisions**

**Point 2.4** The sentences ‘However…in the country.’ and ‘Recent surveillance…in China’ contain the same message. Move sentence ‘Synthetic drug abuse…HIV/other STDs’ to the previous paragraph between ‘Recent surveillance…in China’ and ‘The risk for…new infections’.

We followed the reviewer’s suggestions. The revisions were made in lines 6-10 on the first paragraph of the Introduction section on page 4.

**Point 2.5** I don’t understand the sentences ‘New type drugs have just been sporadically reported in the news media’ and ‘little is known about the types of new drugs’ Which are the new type drugs? MA? According to the first paragraph it seems synthetic drug abuse (MA) has increased dramatically.

It means the synthetic drug abuse has not been draw attention in the public in China, more research is needed to better understand the types of new drugs and its relationship with risky behaviors. Synthetic drugs include several types of drugs such as methamphetamine (MA), ketamine, morphine, and amphetamine. We deleted the sentence. The revision was made in the lines 4 of the second paragraph in the Introduction section on page 5.

**Methods: Major compulsory revisions**

**Point 2.6** It is not clear which potential participants were recruited. Drug users? What type of drug users, in what venues? For example recreational drug users are very different from homeless drug addicts.

The recruitment criteria require that participants be willing to complete the study, and self-report ever using synthetic drugs in the last year. A mixed method of peer referrals, community outreach, and venue-based recruitment were used in this study. The revisions were made in the “Recruitment and Participants” section on page 5.

**Point 2.7** How did the recruitment took place? How many participants were recruited through which recruitment strategy? A flow chart could be informative to present recruitment. Recruitment criterium; participants should be willing to complete the study.
This leads to a selection bias, and should be mentioned in the discussion. How many people were recruited/asked and how many agreed to participate in the study?

Fixed interview location was set up in each city to recruit participants. Peer referrals were the major recruitment strategy. A part of participants didn’t want to visit the fixed interview site due to illegal practice of drug abuse in China, so the trained health professional conducted the interview in community or venues such as, hotel, bar. Recruitment criteria require that participants be willing to complete the study, and self-report ever using synthetic drugs in the last year. We didn’t collect the non-response information in this study, which could be one of limitations of this study. The limitation was noted in the lines 14 on page 11.

Point 2.8 STD examination, which STDs?

We apologize for oversight in the initial submission. Blood sample of all participants were collected for HIV, syphilis and HCV tests, all individuals with the positive results were referred to the health care programs for further examination and treatment. We deleted the sentence of “free STD examination and treatment was provided” in the Method section in lines 9 on page 5.

Point 2.9 This sentence is not clear: ’Drug use is illegal…to consent’. Do you mean participants may have declined to participate or you included participants without an informed consent?

The sentence means the non-response rate in the survey would be increased because drug abuse is illegal in China. Informed consent was received from all eligible participants in our survey.

Statistical analyses

Point 2.10 Calculation of prevalences should be included. Did you test for confounding and effect modification?

We provided a detail in the Statistical Analyses, “The prevalence rates were calculated by demographic characteristics, drug use and sexual behaviors, and utilization of HIV-related prevention services.” in the lines 4 in the “Statistical Analyses” section on page 7. All potential collinearity, potential confounding, and effect modification were examined.

Results: Major compulsory revisions

Point 2.11 Ketamin users is mentioned two times.

The revision was made in lines 4 in the “Result” section on page 8.

Point 2.12 Do not repeat results in text and tables. Only the most important results from the tables can be briefly described in text.
We deleted the univariate analysis content in the lines 17 and 21 in the “Correlates for syphilis, HCV infection and unprotected sex” session on page 8.

Point 2.13 In the Discussion the following is concluded: ‘This study contributes to understanding the emergent role of club drug abuse on the HIV/STD epidemic and its association with risky sexual behavior in the 2 cities of Shandong Province.’ Since, analyses on the association between club drug use and risky sexual behavior was missing, this cannot be concluded. This analysis should be included because it is part of the study objective.

Many thanks for the reviewer’s comments. We made additional analyses on the association between club drug use and risky sexual behavior. A column was added in the Tables 1/2 to describe the status and its correlates of unprotected sex.

Point 2.14 Generally, syphilis is a problem in a specific risk group for STDs; men who have sex with men. Do you have any information regarding sexual preference of the participants? Otherwise, this should be mentioned as a limitation in the Discussion.

This study showed 9.6% participants were infected syphilis, all of them were methamphetamine users and syphilis was independently associated with ever having had sex with commercial sex partners in the past 12 months. Moreover, an alarmingly high prevalence (52.5%) of reported ever having sex with commercial sex partners with 89.9% inconsistent condom use were found among drug users in this study.

Point 2.15 Among drug users, MA use is large, but it is not clear if MA is used as only drug, or in multi drug use. This is important for the conclusion of the study.

In this study, we recruited synthetic drug users, and the results showed 96.6% of all participants were methamphetamine users, 11.9% of all participants reported having ever used ≥2 types of these drugs. This was discussed in the lines 3 in the results section, Drug use and sexual behavior on page 8.

Table 1. Major compulsory revisions

Point 2.16 Table 1 is too extensive. In tables, focus on the most important results for your objective. In this study I would suggest; syphilis, HCV, sexual and drug use behaviors. Multiple determinants can be described in text briefly for example study sites, residency, ever received intervention, ever had a test for HIV, know HIV test result, HIV infection (because of low numbers, n=2).

We simplified Table 1 by removing study sites, residency, ethnicity, ever had a test for HIV and HIV infection. We think that it will be helpful to keep some background information in Table 1.

Point 2.17 Syphilis and HCV positives are duplicate in the table. They are included in
participants (n=805) and are analyzed as a separate group. Change this into syphilis/hcv negative, syphilis positive and hcv positive. Were there persons infected with both syphilis and HCV? This should be mentioned.

There were 11 persons infected with both syphilis and HCV in the study. Table 1 was revised.

Table 2. Minor essential revisions

Point 2.18 I suggest table 2 would contain results of multivariate analysis only. The table would become more clear and accessible for the readers. Results of univariate analysis are already presented in text. The emphasis should be on the results of multivariate analyses.

The revision was made according to reviewer’s suggestion. We deleted some no statistical significance variables in Table 2.

Discussion: Major compulsory revisions

Point 2.19 Drugs were not associated with syphilis infection. Only injecting drug use was independently associated with HCV infection, although it is not clear which type injected drug, probably heroin. This is a main result of the study and should be stated more clearly.

All syphilis cases (77) are methamphetamine users with 2 of them also ketamine and amphetamine users. Drug use is strongly associated with syphilis.

Point 2.20 Independent risk factors for syphilis were female sex, having commercial sex in the past 12 months, with less regular sex partners and co-infection with HCV. No conclusions are made to target syphilis prevention in female sex workers, although this is the most vulnerable group for possible syphilis infection according to your results.

Our previous report (Liao et al. STD 2011) revealed alarmingly high prevalence of methamphetamine use among FSWs. Methamphetamine users were more likely to be single, younger, inconsistent condom users, and have syphilis.

Point 2.21 Independent risk factors for HCV were injecting drug users and co-infection with syphilis. No recommendations for information/prevention programs were made. According to this study, needle sharing of injecting drug users could be a reasonable cause of the HCV infections.

We agree with the reviewer’s comments. We added the point that “Independent risk factors for HCV were injecting drug users and co-infection with syphilis.” “Needle sharing of injecting drug users could be a reasonable cause of the HCV infections.” Other Studies showed that HCV risk increases commensurate with increasing numbers of sex heterosexual partners. We also highlighted that the finding of this study underscore the
needs for further research to better understand the role of heterosexual transmission of HCV among club drug users. We discussed this content in the first paragraph on page 11.

Point 2.22 The sentences ‘China has seen…of Shandong Province’ are well written and should be moved to the Introduction. It represents your study objective more concise than current sentences in the Introduction.

We moved the sentence to the Introduction section in the lines 3-5 on page 4 and lines 6-7 on page 5.

Point 2.23 The sentence ‘This study…sexual behaviors’ is not based on the results of this study. Club drug use (MA?) was not associated with syphilis and HCV. Neither the association between (club) drugs and risky sexual behavior was analyzed, nor the association between (club) drugs and HIV. Rewrite the sentence according to the results of the study.

The sentence was deleted from the first paragraph of Discussion section.

Point 2.24 Extensive use of illegal drugs is the second result.

Many thanks the reviewer’s comments, we rewrite the second paragraph of Discussion section to describe the phenomenon of extensive use of illegal drugs in Qingdao.

Point 2.25 Add reference to the sentence ‘Unprotected heterosexual contacts…a timely fashion’. Add reference to the sentence ‘studies have revealed…heterosexual partners’.

References were added.

Point 2.26 ‘Despite these limitations and possible biases, we feel the data highlight a prevention opportunity that cannot be ignored.’ Think about which prevention opportunities are supported by the results of this study and which prevention opportunities are supported by literature.

The current intervention efforts for substance use in China still focused on heroin, which played an important role in China’s HIV/AIDS epidemic in the past decades, so far no targeted effort tackle the new emerging challenge of club drug abuse. However, unprotected heterosexual contacts has been increasing proportionally in contribution of HIV transmission in China, it is possible that the club drug abuse could further fuel this trend in the nation without better-targeted, effective intervention efforts taking place in a timely fashion.

Point 2.27 Start new paragraph from ‘This study revealed…of the syndemics.’

The revision was made according to reviewer’s suggestion in lines 17 on page 11.

Abstract: Major compulsory revisions
Point 2.28 Replace objective by background and add background information for the study. The objective is not stated clearly. There was no analysis on the type of drugs and its correlates.

The objective was revised to “This study was to investigate the type of drugs, syphilis and hepatitis C virus (HCV) infection and the correlates for syphilis, HCV and unprotected sex behavior with commercial sex partners in the last year among drug users in 2 cities along the east coast of China.

Point 2.29 Explain methods more clearly. What was the study group? What was collected in terms of data and biological samples. Also include the type of analysis.

The revision was made according to reviewer’s suggestion. The method was revised to “With community outreach, venue-based recruitment, and peer referrals, a cross-sectional survey conducted in 2010 provided demographics, sexual and drug use behaviors, HIV knowledge and the utilization of intervention services among drug user. Blood samples were collected for HIV, syphilis, and hepatitis C virus tests.” in the Method in the Abstract.

Point 2.30 Limit results to main results only. Delete sentences ‘All syphilis cases…the last sex’. These are not the main results according to your objective.

The revision was made according to reviewer’s suggestion. We deleted the sentences “All syphilis cases…the last sex.” and added the correlates for unprotected sex behavior in the Result section.

Point 2.31 The conclusion needs to be in line with the main results. For example; Methamphetamine is the predominant drug used among the drug users, although there was no association between MA and syphilis/HCV. The prevalence … Keep in mind which prevention/intervention opportunities are supported by the results of this study.

Thanks for the reviewer’s excellent comments. The revisions were made in the conclusion section.

We also made some editorial changes including some context information in the Background section of the abstract.

Again, we are grateful to the revision opportunity. We are looking forward to your reviewing our revised manuscript. If you have any questions, please feel free to contact Meizhen at liaomz161@126.com/011-86-186-1528-1775 (Beijing time) or yujiang at jiayj@aol.com/615-482-1512(EST).

Sincerely,

Meizhen Liao, MD, PhD
Shandong Center for Disease Control and Prevention

Yujiang Jia, MD, DrPH
Vanderbilt University School of Medicine